Specialty Conference

New Advances in Bone Research

Moderator
HARLAN C. AMSTUTZ, MD

Discussants
ERIC E. JOHNSON, MD; GERALD A. M. FINERMAN, MD; ROY A. MEALS, MD; JOHN R. MORELAND, MD; WILLIAM C. KIM, MD, *and* MARSHALL R. URIST, MD

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine, UCLA School of Medicine, Los Angeles. William M. Pardridge, MD, Associate Professor of Medicine, is Director of Conferences.

In the past 20 years there has been an explosion in developments in the care of musculoskeletal disease. Large segmental defects created by trauma or tumor resections can now be treated with massive allografts. The use of an electrical charge to accelerate bone formation is one of the exciting new developments in orthopedics. Recently developed microvascular surgical techniques enable surgeons to successfully reattach amputated digits and limbs. Equally important are the advances in transfer of vascularized large bone grafts to bridge segmental defects. Total joint replacement has had the greatest impact on the treatment of joint disorders. Although techniques using acrylic fixation have improved, loosening is now the major complication of all long-term acrylic devices. Acrylic-fixed devices have a finite life, deteriorating with time. The hope for the future seems to lie in new methods of fixation using porous ingrowth. One of the most promising adjuncts to bone grafting and potential to enhance ingrowth into porous systems is the use of bone morphogenetic protein. Identification of osteoprogenitor cells and the chemical identification of key elements in a system of osteogenetic stimulation will eventually be clinically available and have far-reaching implications.

The Treatment of Malignant Segmental Defects of Bone—The UCLA Experience

ERIC E. JOHNSON, MD:* The treatment of large segmental skeletal defects is one of the more challenging problems encountered by orthopedic surgeons. Since the late 1800s osseous allograft has been the advocated treatment of large segmental defects that occur from benign or malignant tumors, arthrodesis of joints and repair of traumatic defects. There have been numerous reports in the literature of good to excellent results for the treatment of initially benign tumors and, during the past two decades, of low-grade and high-grade malignant tumors. These techniques have been used at UCLA in combination with doxorubicin hydrochloride and radiation therapy preoperatively and adjuvant chemotherapy postoperatively in attempts to salvage a functioning extremity, control local recurrence and—it is hoped—improve survival.

Allografting began in 1881 when McCewen[1] successfully allografted a defect in a child's humerus. Lexor[2] in 1908 and Inclan in 1942[3] implanted allografts for benign skeletal defects, including osteochondral grafts for joint replacement. As this technique proved to be successful in cases of nonaggressive disease, it was also used in treating low- and high-grade malignant tumors. In 1973 Parrish[4] reported long-term results on 21 patients with benign or low-grade malignant tumors and noted an acceptable success rate. In 1976 and 1982, Mankin and associates[5,6] used allograft in the treatment of malignant or aggressive tumors. Although they noted a significant complication rate, this was acceptable be-

*Assistant Professor, Division of Orthopaedic Surgery, Department of Surgery, UCLA School of Medicine.

(Amstutz HC, Johnson EE, Finerman GAM, et al: New advances in bone research—Interdepartmental Conference, University of California, Los Angeles [Specialty Conference]. West J Med 1984 Jul; 141:71-87)

This study was supported by grants from the National Institutes of Health, US Public Health Service (No. AM 2033 [Dr Kim], and No. DEO 2103 [Dr Urist]).

Reprint requests to Harlan C. Amstutz, MD, Department of Surgery, Division of Orthopaedics, UCLA School of Medicine, Los Angeles, CA 90024.

cause of the technical problems inherent in this type of surgical treatment.

Besides obviating the sacrificing of normal host structures, allografts have certain advantages, including no donor site morbidity and no limit in size, shape or quantity of bone. However, allografting of large defects has several disadvantages, including delayed or incomplete incorporation with normal host bone, fracture or loosening of fixation, infection, possible transfer of disease and extensive laboratory preparation.

As with the transplantation of any tissue, an immunogenic response occurs. Compared with prepared bone, fresh bone allografts stimulate a strong antigenic response. Burchardt and Enneking[7] have shown that freezing (−80°C), freeze-drying or chemosterilizing antigen-extracted autodigested alloimplant ("AAA") bone substantially decreases the antigenicity of a graft. All of the techniques currently used for preserving bone result in a loss of cell viability, but the osseous tissue retains definite biologic potential in regards to stimulating vascular invasion, resorption of old matrix and synthesis of new bone.[8]

The UCLA Medical Center Division of Surgical Oncology, under the direction of Drs T. T. Grant and F. L. Eilber,[9] initially developed a limb salvage protocol consisting of preoperative and postoperative adjuvant chemotherapy, whole limb irradiation and en bloc resection for the treatment of extremity osteosarcoma. Preoperative chemotherapy consists of intra-arterial administration of 30 mg of doxorubicin, which is continuously infused by pump directly into the tumor for 24 hours on each of three consecutive days (Figure 1). Then 350 rads of whole-limb irradiation are given by rapid fractionation for ten days for a total dosage of 3,500 rads. One to two weeks after completing the radiotherapy, surgical resection is done, obtaining a 10-cm proximal margin on all specimens, which is verified by frozen section.

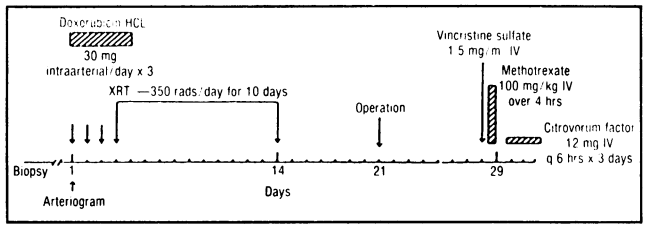

Figure 1.—Preoperative adjuvant chemotherapy and irradiation (XRT) given before resection.

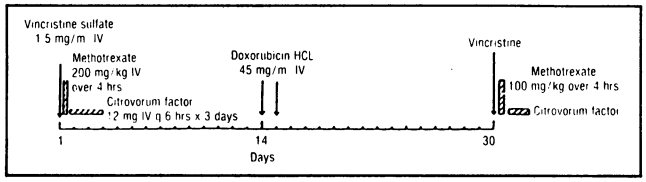

Figure 2.—Postoperative chemotherapeutic regimen.

Postoperative adjuvant chemotherapy is begun two weeks after surgical resection. Doxorubicin is alternated with the combination of vincristine sulfate and methotrexate given intravenously twice a month (Figure 2). Chemotherapy is repeated every two weeks until a maximum dose of doxorubicin of 450 mg per sq m of body surface is achieved. Doxorubicin is then discontinued and methotrexate is given once a month for a year.

The primary goal of this protocol is to permit a functional salvage of the involved extremity by replacing the resected tumor and controlling metastasis and local recurrence. Histologic evaluation of the effectiveness of this protocol shows an average cell viability loss of 98% in all resected tumor specimens.

Between 1975 and 1979, 29 patients with upper and lower extremity osteosarcoma (20 femoral and 9 humeral) refused amputation and underwent resection using the UCLA Limb Salvage Protocol (Table 1). At an average follow-up of 19 months, 12 patients out of 20 with femoral disease survived; at an average follow-up of 2½ years, eight patients out of nine with humeral disease survived.

Initially the freeze-dried or fresh-frozen cadaveric allografts were used in 11 femurs and 7 humeri. One total humeral, one proximal humeral and five distal

TABLE 1.—*Characteristics of 29 Patients With Osteosarcoma Who Underwent the UCLA Limb Salvage Protocol, 1975-1979*

Site	*Sex* ♂	♀	*Average Yrs*	*Survival*	*Average Follow-up*
Femur	12	8	20.2 Range, 12.0-47.2	12/20	19 mos Range, 8.6 mos-3.8 yrs
Humerus	6	3	18.9 Range, 16.0-31.6	8/9	2.5 yrs Range, 7.0 mos-3.4 yrs

TABLE 2.—*Operative Procedures in 29 Patients With Osteosarcoma Who Underwent the UCLA Limb Salvage Protocol, 1975-1979*

Site	*Allograft IM Rod PMMA*	*Giliberty plus Allograft*	*Endoprosthesis*	*Total Femur*	*Arthrodesis*	*Amputation*	*Total Operations*	*Total Patients*
Femur	10	1	6	2	2	3	24	20
	Extensive Resection plus Allograft	*Total Humerus*	*Middle ⅔ Resection plus Allograft*	*Endoprosthesis*	*IM Rod plus Allograft*	*Excision Allograft*	*Total Operations*	*Total Patients*
Humerus	5	1	1	1	1	1	11	9

IM = intramedullary
PMMA = polymethyl methacrylate

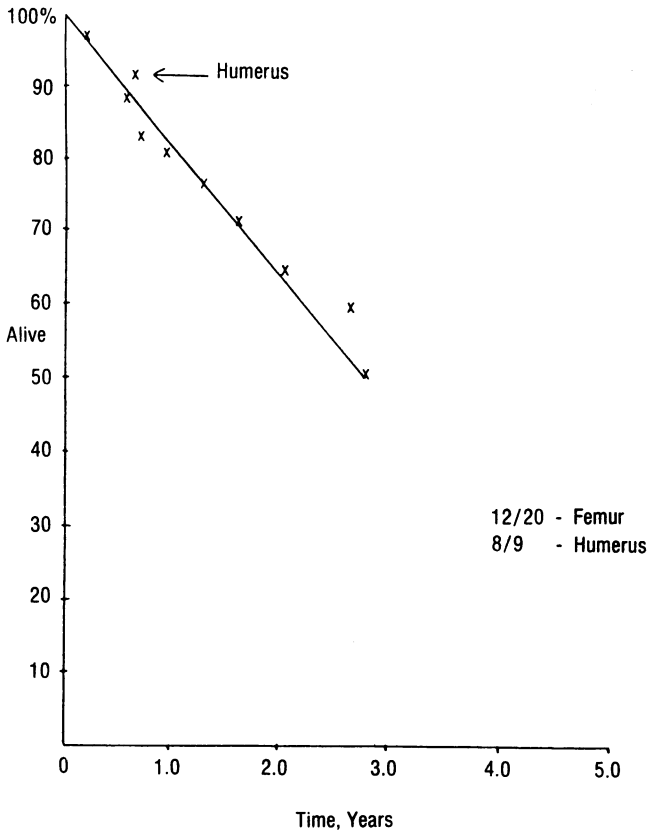

Figure 3.—Percentage of survival versus time after initial operative procedure for osteosarcoma limb salvage.

femoral endoprostheses have been used during the past 1½ years of this study. Two patients underwent resection arthrodesis of the knee, and two patients had total endoprosthetic femoral replacement (Table 2). All allograft replacements failed because of fracture, infection, loosening of fixation and nonincorporation with host bone (the last type of failure is most likely related to soft tissue changes resulting from adjuvant chemotherapy and irradiation). Endoprosthetic replacement also carried the risk of loosening, fatigue fracture and infection; however, follow-up to date of this mode of therapy has not been long enough to evaluate failure rates.

The patients were examined for muscle strength and range of motion, pain with rest and ambulation and evidence of local recurrence. The femoral allografting and endoprosthetic replacements were mainly done for distal femoral disease. Muscle strength was decreased about two grades in the quadriceps and hamstrings and about one grade at the ipsilateral hip. This decrease was related to a combination of the amount of tissue resected and the postoperative irradiation. The lower extremity range of motion was decreased from 25% to 40% at the hip and about 74% in knee flexion as compared with a normal extremity. In the upper extremity, most of the lesions involved the proximal humerus. Because of the amount of soft tissue resection required, muscle strength decreased about three grades at the shoulder and two grades at the elbow. The range of motion was significantly decreased in the shoulder, ranging from 67% to 80% in the modes of flexion, extension, abduction and internal and external rotation, and a decrease of 30% to 40% of the elbow range of motion. Postoperative pain was surprisingly nonexistent. Patients had a pain rating on the UCLA pain scale of 9 out of 10 for the femur (10 being pain-free) and 9.5 out of 10 for the humerus. Secondary procedures of the humerus and the femur basically dealt with the treatment of wound coverage and infection. The complication rate was between 25% and 40%. Major complications included allograft fracture, deep and superficial infection that loosened fixation and nerve palsy.

The projected survival in the osteosarcoma limb salvage program seems to be linear, with about 50% of patients alive at the three-year follow-up (Figure 3). At an average follow-up of 2½ years, eight of nine patients with osteosarcoma of the humerus survived; of patients with osteosarcoma of the femur, 12 of 20 survived. In 29 patients, there was one local recurrence, which was probably due to inadequate resection of an intraarticular extension of the tumor margin at the time of operation. No evidence of skip lesions was found in any of the resected tumors inspected for abnormalities.

Summary

Wide-block excision of bone tumor is a viable technique but does carry a significant risk of postoperative complications. The use of allograft in combination with chemotherapy and irradiation does not seem to be a successful mode in the treatment of these skeletal defects. Endoprosthetic replacement when combined with chemotherapy seems to provide an alternative to allografting. Other authors have reported good to excellent results in resecting large tumors without the use of chemotherapy, but the local recurrence rate is significantly higher than that experienced with the UCLA protocol.

Preoperative intraarterial administration of doxorubicin and radiation therapy have a dramatic effect on tumor histology and seem to improve the control of local recurrence. The use of metallic endoprosthetic replacement when combined with chemotherapy and irradiation offers a viable choice to allografting, but does have potential and definite failure rates associated with total joint replacement. Function of the extremity involved is significantly limited in strength and motion but is accepted by patients. The overall survival rate does not seem to be jeopardized by en bloc resection, which, when used in conjunction with chemotherapy, appears to control local recurrence of the tumor.

The Application of Electrical Stimulation in Orthopedic Operations

GERALD A. M. FINERMAN, MD:* In 1953 investigators noted that electrical charges could be measured when forces were applied to bone. These charges were termed

*Professor of Orthopaedic Surgery, Department of Surgery, UCLA School of Medicine.

stress-generated potentials and were not dependent on cell viability. Areas of bone under compressive loads had a negative electrical charge, whereas areas under tensile forces had a positive electrical charge. It has been hypothesized that changes in electrical potentials are an important stimulus to bone formation and resorption in response to mechanical stresses as described by Wolff's law. Further investigation identified bioelectric potentials, which are dependent on cell viability. Areas of bone growth are electronegative; inactive areas are either electrically neutral or electropositive. Measurement of electrical charges in single osteons has shown the change in potential to be related to the application of tensile or compressive stresses. The cellular mechanisms by which electricity affects bone are not well understood. However, it has been suggested that electricity affects the cell membranes to increase production of adenosine 3′:5′-cyclic phosphate modulating basic cellular functions.

These observations have led investigators to apply electrical charge to bone in attempts to induce bone formation and thereby heal nonunions. In the first method devised by Brighton and colleagues,[10] they applied a negative charge at the fracture site by placing an electrode percutaneously. An external power source was applied and 20 μA of current provided for a 12-week period. This technique was termed semi-invasive, requiring a slight surgical procedure; it required, however, careful placement of the electrodes and care to avoid infection around the electrodes.

The second technique is that of implanting an entire unit, including the power supply and electrodes, and removing it surgically after the power supply fails. This method permits precise placement of the electrode but requires two surgical procedures and reoperation if the power source fails.

The third clinical method, developed by Bassett and co-workers,[11] induces a current in bone by placing a Helmholtz coil, which generates a pulsating electromagnetic field, about the fracture site. The pulsating electromagnetic field induces an electrical field at the nonunion site. Although this method is noninvasive, it requires a bulky nonportable device that must be connected to fixed power sources.

A fourth method being developed by Brighton and associates makes use of capacitive coupling to induce an electrical charge in bone. This technique, being noninvasive and portable and thereby assuring patient compliance, is under clinical investigation.

Brighton and colleagues[10] have reported their results using the semi-invasive application of a direct 20-μA current in the treatment of 258 patients with nonunion at varying sites. In their multicenter study, 80% of patients with nonunions had healing. Bassett and coworkers[11] have also reported their results using noninvasive pulsating electromagnetic fields in 125 patients with nonunion of the tibia. In their study, 87% of patients had healing of their nonunions. Both investigators found that synovial pseudarthrosis failed to heal. Resection of the jointlike surfaces was necessary for healing to occur. This type of nonunion can be identified by a cleft between the bone fragments on bone scan with bone-seeking radionuclides.

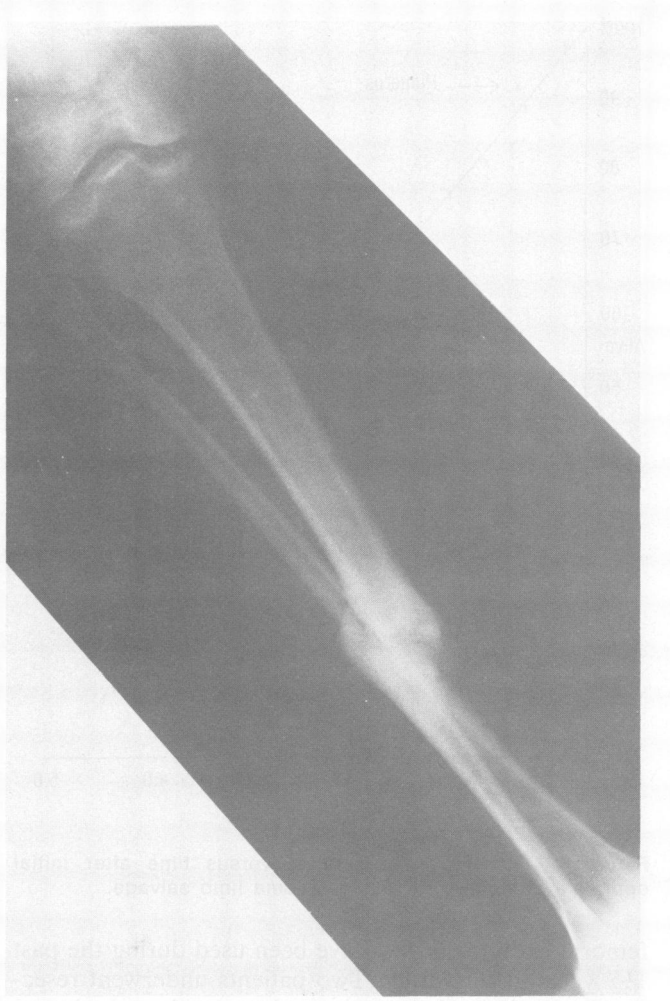

Figure 4.—X-ray examination 19 months postfracture shows nonunion of tibia, with hypertrophic callous formation and varus deformity.

Report of a Case

I will present a case history to illustrate the use of electrical stimulation for the treatment of nonunions. The patient, a 25-year-old draftsman, was initially injured in 1977 when his motorcycle was struck by an automobile. He sustained a fracture of his femoral neck and midshaft femur and a compound fracture of the tibia and fibula. The tibial fracture was debrided and the patient placed in traction. Two weeks later the patient underwent open reduction of his femoral fractures and the insertion of Kirschner wires into the tibia with cast immobilization. The femoral fractures healed; the tibia, however, did not.

At his first UCLA visit 19 months postfracture, the tibial skin wounds had healed and the tibia had shortened by 2 cm. There was motion at the tibial fracture site and the patient had a 10-degree varus deformity. X-ray examination (Figure 4) showed nonunion with hypertrophic callus and varus deformity.

At 21 months postfracture, the patient underwent a

surgical procedure to have a Wagner external immobilization apparatus inserted for correction of his deformity, to osteotomize the fibula and to have electrodes inserted for semi-invasive direct-current stimulation. X-ray films showed the Wagner apparatus and electrodes in place with correction of the varus deformity (Figure 5). Electrical stimulation was maintained for three months along with immobilization in the Wagner apparatus. The patient was placed into a patella-tendon-bearing cast for an additional three months until fracture healing could be definitely determined radiographically. An x-ray examination at about two years after electrical stimulation showed fracture union, early tibial remodeling and correction of deformity (Figure 6).

The clinical use of an electrical charge to accelerate bone formation is in its early development phase. Investigation of the basic processes by which electrical charges modulate cellular activity in bone is necessary before we realize its full potential. The application of electrical charges may be helpful in fracture healing, prosthetic fixation and treating bone resorption, osteonecrosis, osteomyelitis, limb length inequality and metabolic bone disease, such as osteitis deformans.

Vascularized Bone Transfer

ROY A. MEALS, MD:* Microvascular surgical techniques developed recently have made it possible to replant amputated limb parts and to transfer living tissue from one area of the body to another. Vascularized bone transfers are one such example.

Reconstruction of large bone defects has traditionally proved to be difficult for several reasons. The osteogenic cells in a conventional (devascularized) bone graft survive solely by diffusion until new capillary ingrowth occurs. This means that at best only a few cells survive within the rigid crystalline structure of the bone and that the graft is slowly incorporated into the spanned defect by a process known as "creeping substitution." This term accurately acknowledges that a standard bone graft provides only a calcium framework on which cells migrating from adjacent tissues proliferate and revitalize the bone. The process of "creeping substitution" takes many months or years. Until it is complete and the bone has been entirely revitalized, the graft is structurally unsound and prone to infection.

Using microsurgical techniques, it is feasible in many

*Assistant Professor of Orthopaedic Surgery, Department of Surgery, UCLA School of Medicine.

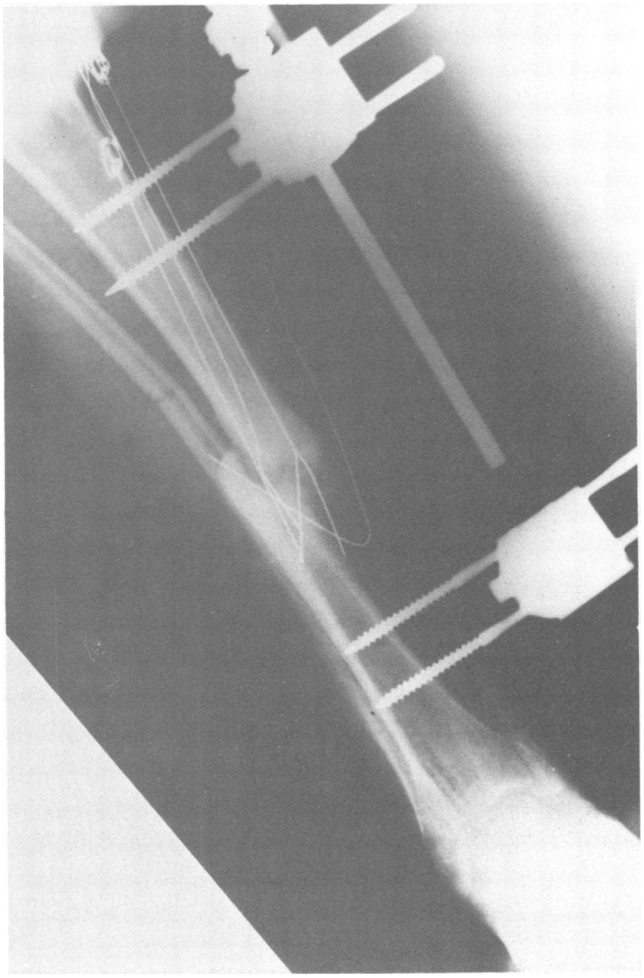

Figure 5.—Photograph of x-ray showing Wagner apparatus and electrodes in place.

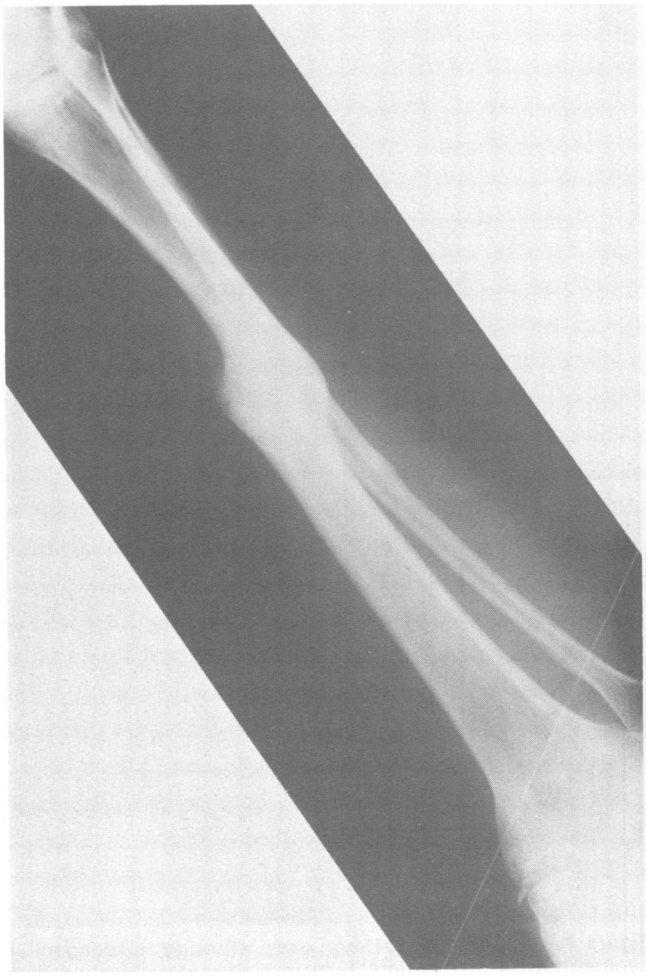

Figure 6.—X-ray examination shows fracture union and early tibial remodeling, about two years after electrical stimulation.

cases to circumvent the problems of traditional bone grafting when reconstructing large segmental skeletal defects. Donor bone can be harvested from one of several favored sites where the nutrient vessels can be isolated with the bone segment. When the bone is transferred to its recipient site, the nutrient vessels can be anastomosed to local vessels and thereby provide immediate blood flow to the transferred bone. The transferred cells survive fully because their blood supply is only temporarily interrupted, and the bone, therefore, maintains its resistance to infection and mechanical stress. The body "sees" the reconstruction as only several "fractures" in living bone; the skeleton is restored as soon as fracture healing occurs between the transfer and the bone ends of the recipient. Thus the reconstruction process is shortened by many months.

Three donor sites are used for vascularized free bone transfers. The posterior rib along with its intercostal artery and associated veins provides a somewhat short and curved bone segment, but has proved to be useful for mandible reconstruction. A segment of fibula, up to 40 cm in length, is the most versatile strut type of free bone transfer using the vasculature supplied from the peroneal artery and associated veins. A segment of iliac crest, transferred with its internal circumflex iliac artery and associated veins, can provide a plate of bone of varying dimensions. Each of these donor sites can be closed with very little functional or cosmetic morbidity to a patient.

In the recipient bed the transferred vessels are anastomosed to available local recipient vessels. Because the transferred bone brings most of its own blood supply, this bone can survive in irradiated or mechanically scarred beds. Diffusion of nutrients from surrounding healthy tissue is unimportant compared with the demands of a conventional bone graft.

Because the technique requires meticulous dissection of the donor bone to avoid injury to its vascular supply, and because it requires careful connection of the vessels that may be as small as 0.5 mm in diameter, the surgical procedure takes many hours and is not the panacea for skeletal reconstruction. General indications include segmental long-bone loss of 6 cm or more, and shorter seg-

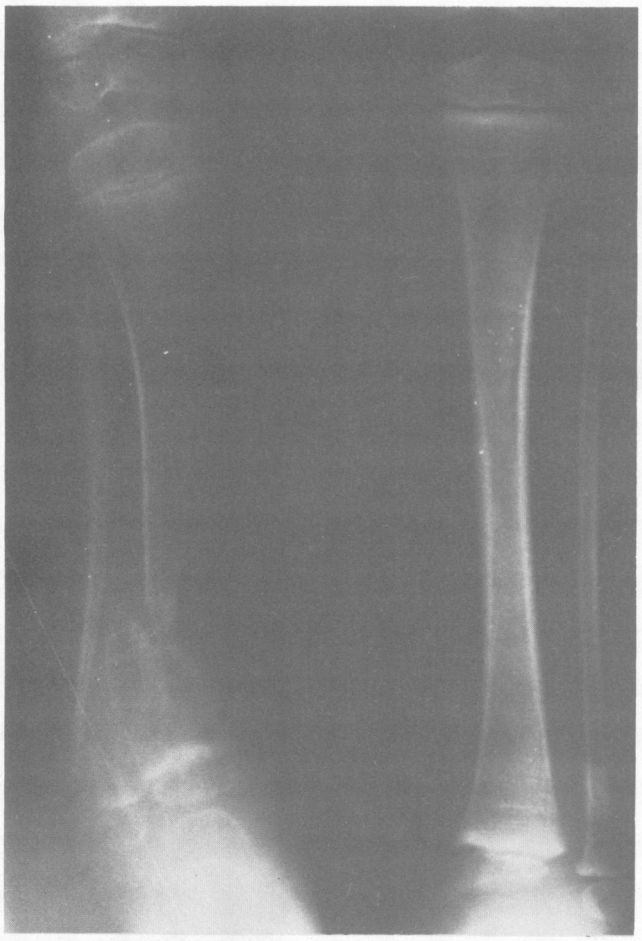

Figure 7.—Photograph of an x-ray showing a congenital pseudarthrosis of the right tibia in a 2½-year-old child that has not healed after multiple bone grafting and electrical stimulation procedures.

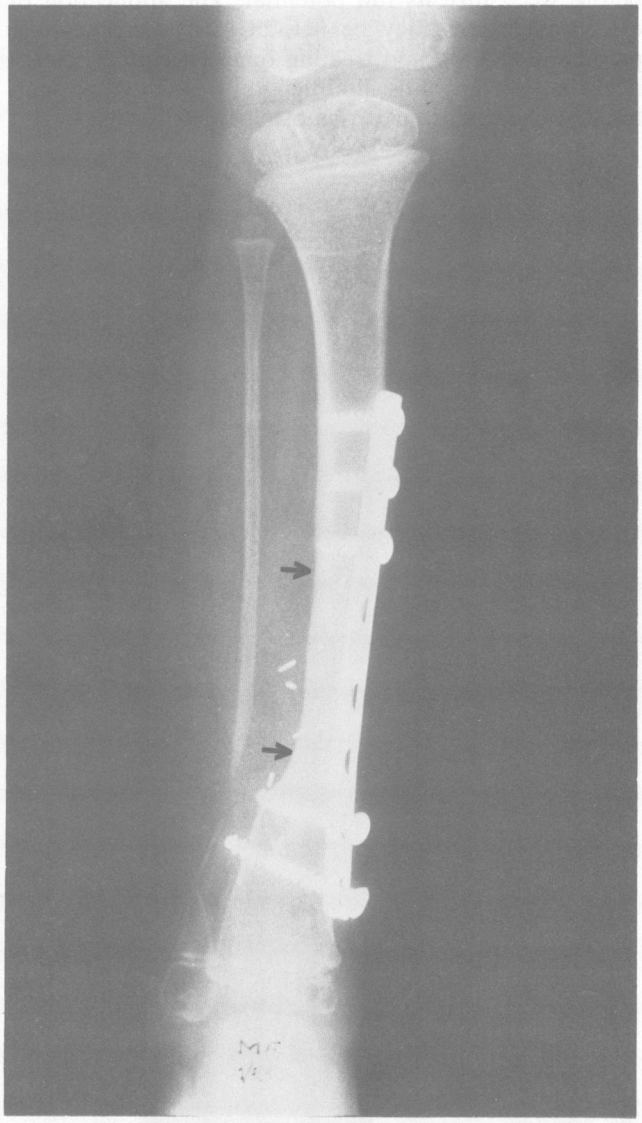

Figure 8.—By six months after operation the vascularized fibula transfer from the left leg (of the patient in Figure 7) has solidly healed at both ends **(arrows).**

mental bone loss that has been resistant to less complicated reconstruction efforts. Conditions for which free vascularized bone transfers have been successfully used include reconstruction for congenital tibial pseudarthrosis and traumatic nonunion of the tibia, femur or humerus, with or without infection.[12] Vascularized bone transfers are also used for long-bone reconstruction after segmental excision of benign but aggressive tumors, as well as low-grade malignant tumors such as giant cell tumor, adamantinoma and chondrosarcoma.[13]

A representative case is a 2½-year-old child who had congenital pseudarthrosis of the tibia that had failed to heal after conventional bone grafting and electrical stimulation techniques were applied (Figure 7). The traditional resolution of similar cases of resistant pseudarthrosis has been to amputate below the knee and to fit with a prosthesis. Preoperative arteriograms confirmed a normal vascular supply in both the donor and recipient legs. A 6-cm segment of fibula from the uninvolved lower limb was removed with the peroneal vessels and the nutrient vessels branching into the bone segment. This bone segment was transferred to the pseudarthrosis site in the involved leg, and the donor peroneal vessels were anastomosed to the recipient anterior tibial artery and associated vein. The limb was internally stabilized with a plate and screws. The procedure took eight hours. Bone scans done on the fourth postoperative day showed rapid isotope uptake in the transferred bone, indicating that its blood supply was intact. By six months after the operation, the graft had united to the tibia at both ends and was beginning to hypertrophy to meet the child's weight-bearing demands (Figure 8).

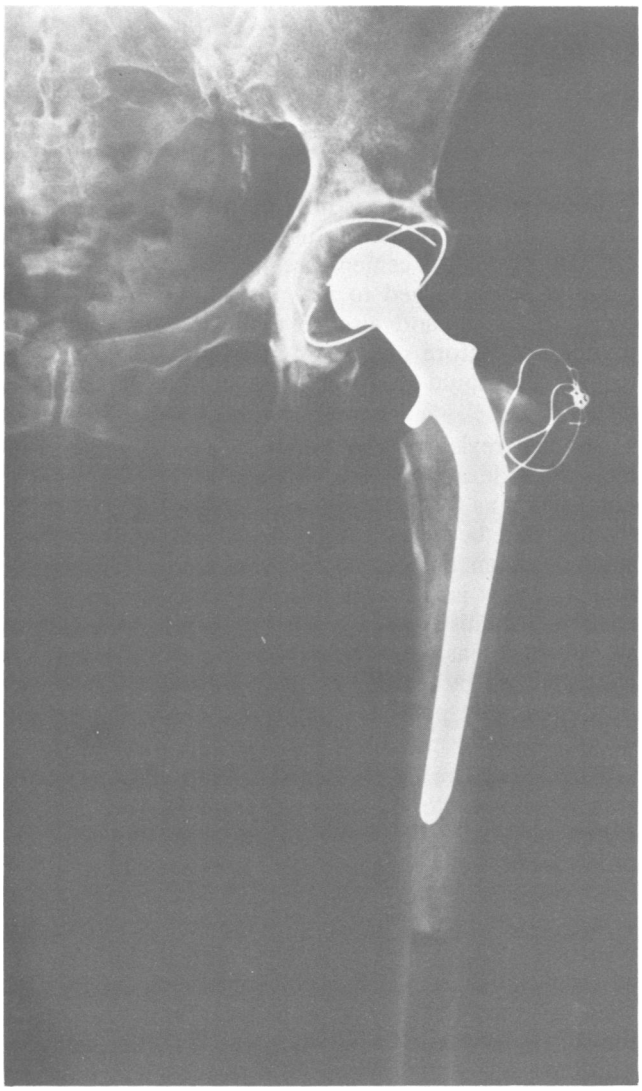

Figure 9.—A Charnley total hip replacement in a 60-year-old woman with osteoarthritis.

Advances in Joint Replacement Fixed With Acrylic Cement

Total Hip Replacement

JOHN R. MORELAND, MD:* In 1962 Sir John Charnley of England developed modern total hip arthroplasty.[14,15] He replaced the femoral head and neck with a small metallic head and neck attached to a metallic stem, which was then fixed in the femoral intramedullary canal with methyl methacrylate cement (Figure 9). The surface of the acetabulum was replaced with a thick piece of high-density polyethylene, also fixed to the bone with methyl methacrylate. This design concept represented a quantum leap in the surgical ability to give a patient with arthritis of the hip consistent pain relief with excellent range of motion; this procedure has remained basically unchanged during the 20 years since. Charnley called his operation "low friction arthroplasty of the hip." The coefficient of friction between the highly polished metal ball and the polyethylene acetabular component is low. The frictional torque applied to the acetabular component is directly proportional to this coefficient of friction and to the metal ball radius. This frictional torque can cause failure of the methyl methacrylate fixation. Small head sizes are thus used to minimize the frictional torque transmitted to the acetabular component.[14,15]

An estimated 75,000 total hip replacements are done yearly in the United States. Significant relief of pain without serious complications occurs in more than 90% of cases. This success rate has been higher than with either cup arthroplasty or femoral osteotomy. Teflon initially used in acetabular component material of total hip replacements had a high wear rate and it was feared that wear would also be a problem with polyethylene. High-density polyethylene currently used for the acetabular component has an extremely low wear rate along with its low frictional property. Wear has not been a clinical problem with polyethylene.[16]

Fatigue fracture of the metallic stem has occurred at a low rate but with higher strength alloys a larger margin of safety has now been provided. Infection occurs in about 1% of previously unoperated hips and is a serious complication because it usually requires removal of the prosthetic components before the infection can be controlled. Dislocation of the compo-

*Assistant Professor of Orthopaedic Surgery, Department of Surgery, UCLA School of Medicine.

nents, which is more likely in the perioperative period, can usually be treated by closed reduction and then careful positioning until the hip forms mature scar in the periprosthetic space. Repeated dislocations usually indicate inappropriate positioning of the components and may require surgical revision. Some patients, particularly men with osteoarthritis, have the complication of heterotopic bone forming in the periprosthetic space. This bone formation results in restriction of hip range of motion but only occasionally causes pain. This bone can be resected later and its reformation inhibited by diphosphonates and irradiation. Nerve palsies have occasionally occurred postoperatively but most resolve.[17]

The major long-term complication of hip replacement operation is loosening of the implants. The prostheses are fixed to the bone with methyl methacrylate cement, which acts not as a glue but as a grout. The fixation is achieved by multiple small mechanical interdigitations of the cement into trabecular irregularities. With time and stress, this initially achieved fixation can fail, with resultant loosening of the components. The movement of the prosthesis-cement composite against the bone may eventually cause pain and sometimes incites a histiocytic and macrophagic response so that bone resorption also occurs over and above what would be expected from mechanical abrading away of bone by the loosened prosthesis. The individual tendency for bone resorption with loosening varies. This loss of bone stock makes surgical revision more difficult because of the lack of firm bone on which to recement a new prosthesis.[18,19]

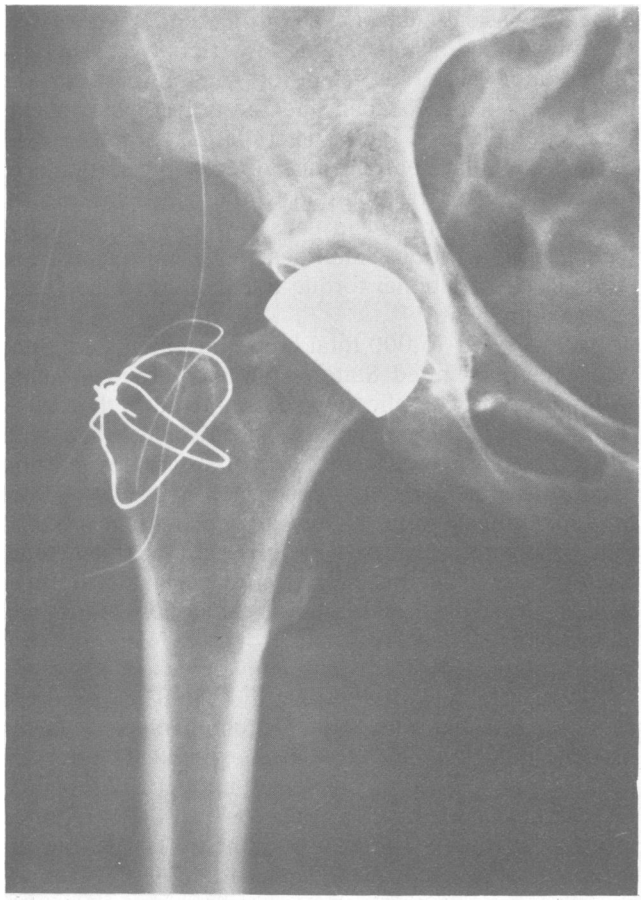

Figure 10.—A surface hip replacement in a 52-year-old woman with osteoarthritis.

The revisional rate in a series of 444 replacements followed for a mean of four years at UCLA was 1.1% for the acetabulum and 2.7% for the femoral component.[19] Charnley reported in a series with 12- to 15-year follow-ups 0.9% acetabular and femoral revision rates.[16] Most other large centers report similarly low revision rates. Several researchers have scrutinized follow-up x-ray films for signs of loosening and have radiologically found a high incidence of loosening. Most hips that show signs of loosening by x-ray study are not symptomatic enough to necessitate surgical revision. Factors contributing to loosening are the duration of follow-up, the degree of stress placed on the implant and the quality of the initial surgical procedure.

Because aseptic loosening is the main cause of failure of hip replacements, efforts have been made to improve the technique of cementation. By obtaining better cement interdigitation into the bony trabeculae, a more durable fixation results. Pulsating lavage and brushes have been used to clean the bone before cementation. Bleeding has been minimized through the use of hypotensive anesthesia and careful attention to hemostasis. To increase cement interdigitation, pressurized cement in a low viscosity state is now used. Handling low viscosity cement requires the use of cement guns, which are also useful for cement pressurization. The femoral canal is now plugged to prevent migration of cement down the canal and also so that the cement can be pressurized before prosthesis insertion. These modern techniques should result in more durable hip replacements.[20]

Surgical revision is becoming more and more common. The durability of a revision hip replacement is not as good as that of a hip replacement being done for the first time because of the increased complexity. Bone stock loss can eventually preclude reconstruction and thus a patient is left with a hip joint supported by soft tissue scar. This type of hip is referred to as a Girdlestone arthroplasty or a resection arthroplasty and is characterized by a short extremity that is unstable but only minimally painful. The patient usually needs one or two walking aids for ambulation.

During the late 1970s, both here and abroad, several researchers developed a new type of hip replacement called surface replacement arthroplasty.[21] In this type of hip replacement, the head and neck are not resected; rather, the head is simply covered with a metal shell cemented in place (Figure 10). The acetabulum is then resurfaced with a thin polyethylene shell. This type of arthroplasty preserves femoral bone stock, making revision of the femoral component easier. It was hoped that this arthroplasty would be more durable than conventional hip replacement. Multiple centers have reported high failure rates with this prosthesis due to femoral and acetabular loosening as well as femoral

neck fractures, but this has been primarily due to its use in youthful and hence more active patients and those with deficient bone stock. The technique is also demanding and at present its use is confined to a few centers.[21] The best indications are in middle-aged patients with osteoarthritis or other patients with arthritis and good bone stock.

Total Knee Replacement

Total knee replacements followed quickly in the United States after hip replacement was introduced around 1970.[22] The initial hip replacement results were so promising that many researchers were inspired to design and to test different knee prostheses. These first knee replacements were not as durable or as reliable as hip replacement because of frequent tibial loosening, patellofemoral pain (because it was usually not replaced), poor range of motion and instability. Hinge knee replacement was particularly unsatisfactory: a high incidence of loosening occurred due to high forces transmitted to the cement bone interface because of the linkage. Infection was also higher with the hinge prostheses.

In the late 1970s condylar type knee replacements were developed.[23] With these designs, all of the articular cartilage surfaces of the femur, patella and the proximal tibia were basically resurfaced with surfaces more similar to the contours of an anatomical knee than the earlier devices (Figures 11, 12). Thus, in most modern knee replacements the patella is resurfaced with a cemented piece of polyethylene (Figure 13). The patellar component articulates with the metal of the femoral component during knee range of motion. The knee components are fixed to the bone with methyl methacrylate cement in a similar manner to that of hip replacements. Many knee replacement surgeons feel that modern knee replacement is as successful as hip replacement.

Tibial component loosening was one of the major early problems of knee replacement procedures. This problem has been minimized by using tibial components that have a short central peg and cover the entire proximal cut surface of the tibia, thereby resulting in a stronger composite structure. As knees become arthritic, many deformities of genu varum or genu valgum develop. If prosthetic knees are left with this deformity, an overload results in the compartment of the knee that is on the concavity of the deformity. If correction of the knee deformity is done at the time of operation, a more durable prosthetic reconstruction is obtained. Restoration of alignment is now one of the major goals of knee replacement, using techniques of ligament release but preserving stability.

Other Major Joint Replacements

Shoulders have been replaced with similar types of materials using a polyethylene component and a metal humeral component (Figure 14). Various designs are available. Pain relief has been achieved but results are

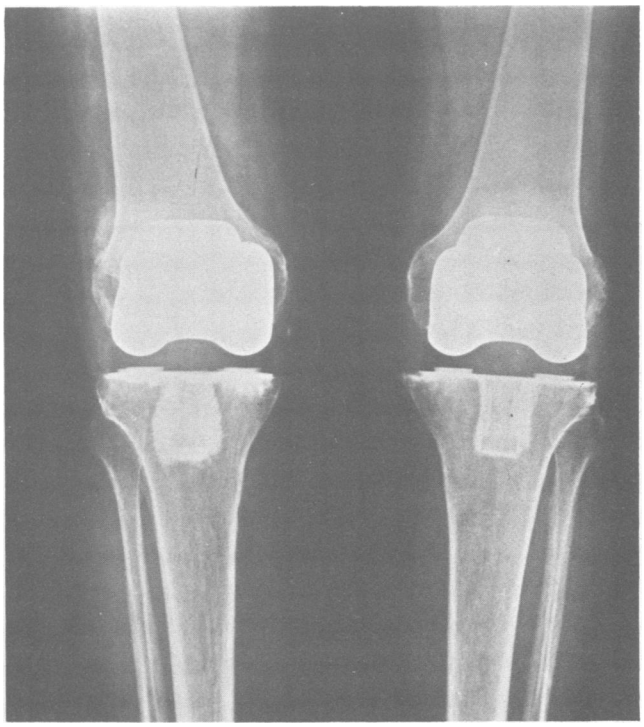

Figure 11.—Bilateral total knee replacement in a 67-year-old man with rheumatoid arthritis.

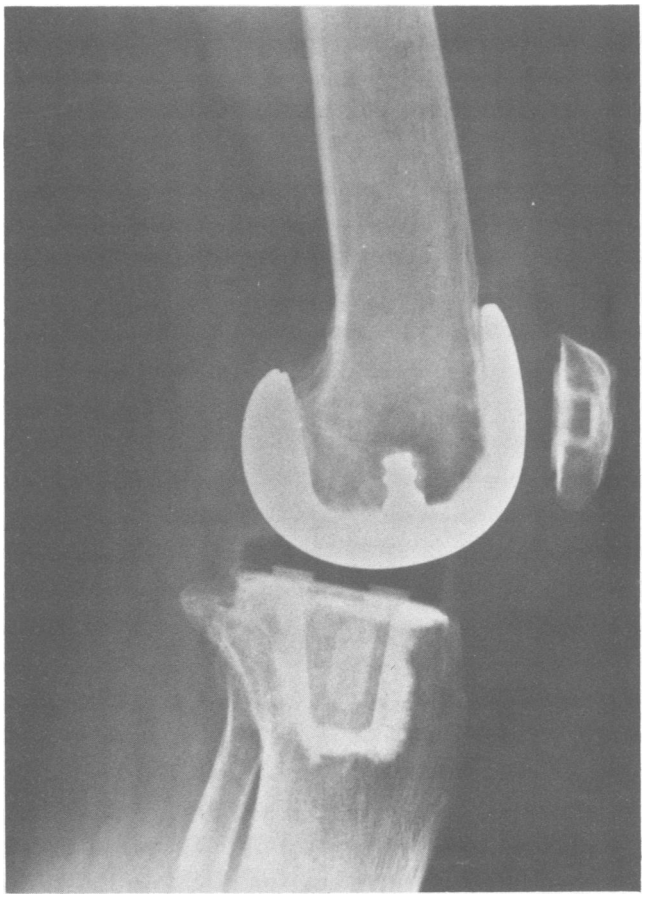

Figure 12.—A lateral view of a total knee replacement.

not as satisfactory when there is a deficient rotator cuff or bone stock loss after trauma. The best results have been in cases of osteoarthritis and osteonecrosis. Patients who have cuff deficiency are placed in a "limited goals" category of providing pain relief.[24]

The many replacement versions developed for ankles have had a high incidence of aseptic loosening, instability and poor range of motion. When aseptic loosening occurs in an ankle replacement, surgical revision is difficult; fusion is also difficult because of a loss of bone stock. An alternative operation, ankle fusion, gives a good functional result. These considerations have limited the indications for ankle replacement to patients with rheumatoid arthritis.

The elbow has also been replaced with metal and polyethylene devices fixed with acrylic. Several different prostheses are available. The major problems with elbow replacement procedures have been instability and loosening. Indications for this operation are infrequent and again primarily restricted to patients who have rheumatoid arthritis.

New Method of Fixation—Porous Ingrowth

WILLIAM C. KIM, MD:* The most common and perplexing complication of cemented total joint replacement is delayed loosening at the bone-cement interface. Loosening is a serious problem because it leads to progressively increasing pain, abnormal joint function and joint-supporting bone loss. Revision of a total joint replacement may be required, heralding repetitive and accelerated cycles of loosening and revisions of diminishing durability. Loosening is a major unsolved problem in cemented total joint replacement.

The pathogenesis of loosening may be conceptualized as time-related loss of mechanical interlock between bone and cement achieved at operation. Fixation failure occurs when stress (force per unit area) exceeds strength of bone-cement interface. The stress for failure may be a single large impact load but is usually the result of a cumulative effect of smaller loads exceeding the fatigue properties of both the bone-cement composite and biologic reparative ability. The failure threshold is modulated through biologic response to transmitted interfacial stress and biocompatibility properties conferred by material, structure and spatial relation of bone and the cemented implant. Stress characteristics outside the physiologic range exaggerate normal bony remodeling according to Wolff's law.[25] Bone hypertrophies at interface points where transmitted stress is excessively high (stress concentration); bone resorption occurs where stress is abnormally low (stress shielding) (Figure 15). Cement is the biomechanically weak link in the bone-cement-implant composite. Its deformation characteristic is mismatched with bone and implant; uneven stress transmission is amplified by uneven cement layers and unstable bone-cement interdigitation, predisposing to loosening.

Under the best of mechanical circumstances, cement tends to activate a thin interfacial fibrous membrane response, indicating a degree of bioincompatibility. This is true even in strong and stable bone-cement interface, which will endure if it is stable.[26] Interfacial motion enhances this response; its thickness and organization parallel the magnitude and direction of motion. With significant loosening, abrasive metal, polyethylene and cement particles incite foreign body histiocytic and giant cell reactions, which in turn seem to mediate interfacial osteoclastic bone resorption (personal observation).

The biomechanical factors pertinent in loosening may be minimized by careful patient selection, assessment of the underlying joint disease and improved implants and surgical techniques. In time, however, an increasing number of cemented total joint replacements is predicted to loosen. That bone-cement fixation system has finite durability, especially in young active patients, is evidenced by a 57% failure rate at five years in patients younger than age 30 years.[27] A more durable

*Assistant Professor of Orthopaedic Surgery, Department of Surgery, UCLA School of Medicine.

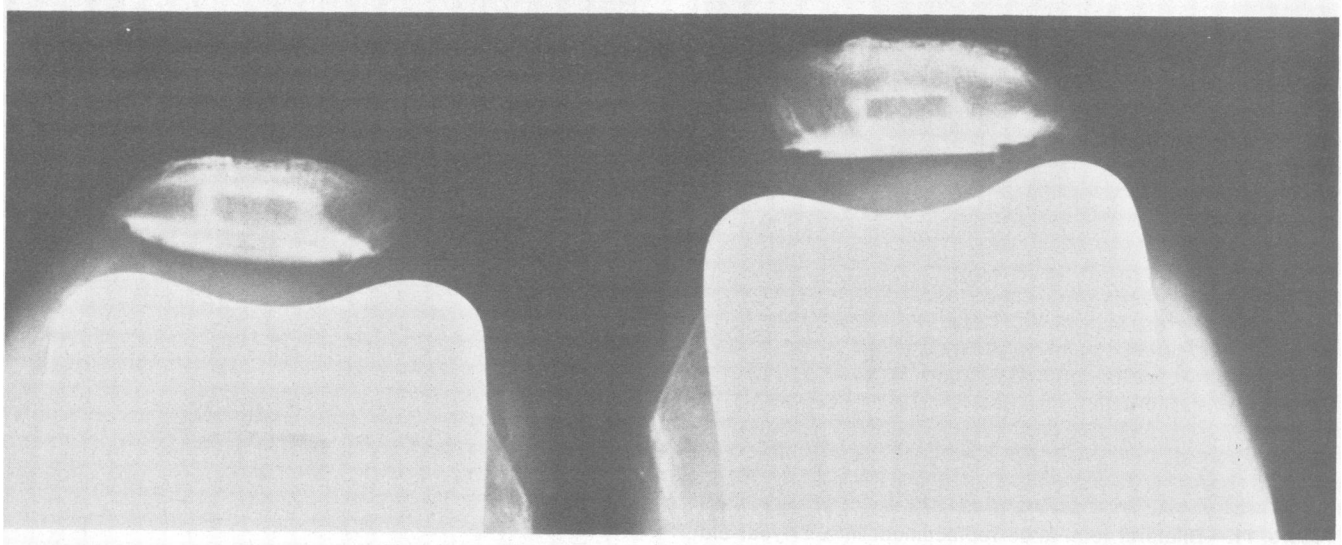

Figure 13.—A sunrise view of total knee replacements.

fixation system is needed, especially in the youthful population, because no major improvement in the bone-cement system is likely.

In the early 1970s an alternate system for fixing bone and implant seemed promising: bone-implant fixation by bone growing into porous-surfaced implants.[28-30] Although it was theoretically more physiologic and supported by laboratory data, the phenomenal early benefit brought to many patients by the cemented total hip replacements probably delayed refinement and clinical application of the porous-ingrowth fixation system. A significant incidence of late bone-cement loosening has now encouraged its serious consideration as an alternative.

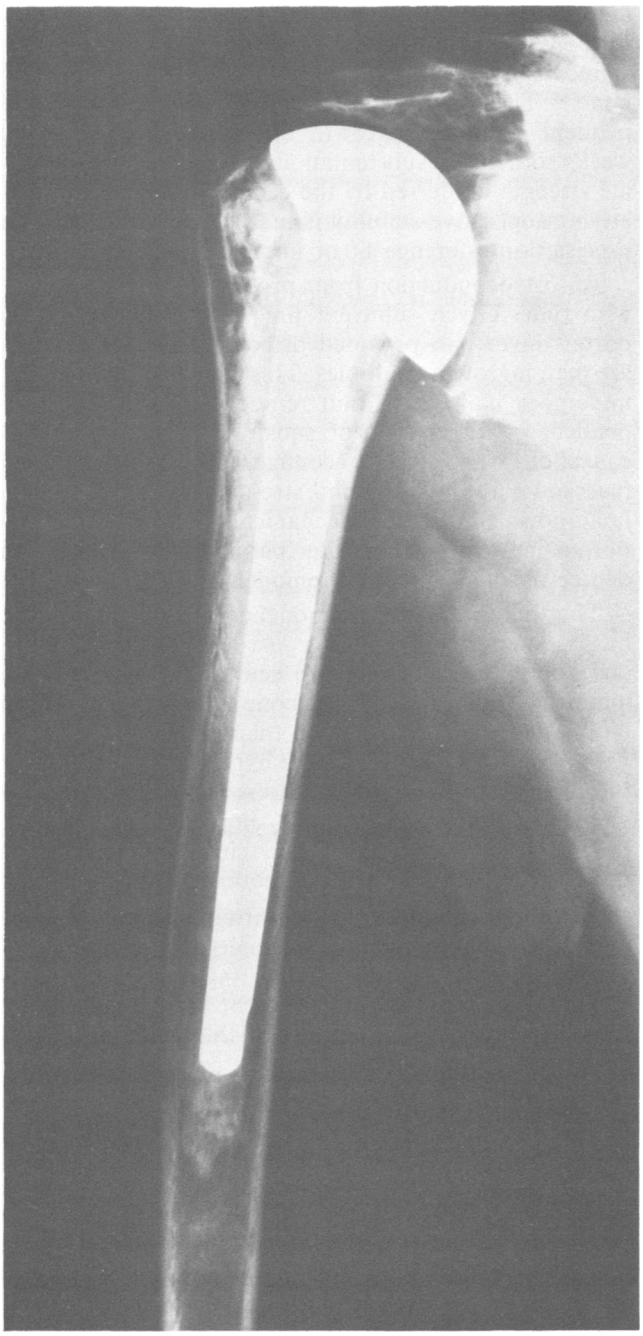

Figure 14.—A total shoulder replacement in a 70-year-old woman with osteoarthritis.

The evolution of porous-ingrowth systems to the present clinically applicable state was one of understanding biologic and mechanical requirements for strong and durable porous fixation. The area of elucidation required technologic advances in implant material, design and fabrication consistent with biomechanical principles governing interfacial stress and biologic response.

The phenomenon of bone ingrowth is incompletely understood but the mechanism is an expression of healing and maturation and a remodeling response to a porous-surfaced implant. The initial event is osteoconduction, the intrinsic drive of bone to grow into a juxtaposed porous network of suitable material and configuration. The ingrown bone then undergoes maturation and remodeling, sustained and directed by interfacial stress transmission characteristics. Osteoconduction has four established requirements: viable bone, biocom-

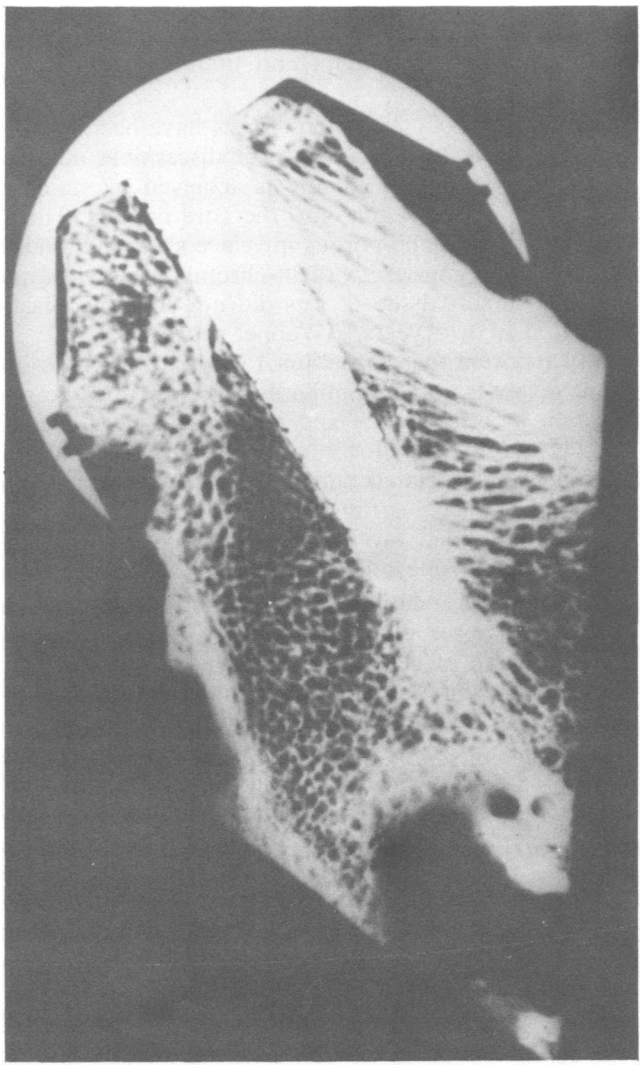

Figure 15.—Stemmed femoral component: Stress preferentially follows paths of greatest stiffness. At sites of stress concentration bone hypertrophies; at sites of stress shielding, bone resorption occurs.

patible material, a range of optimal pore size and intimate and stable apposition of bone-porous interface.

Bone ingrowth by definition requires viable bone. Local and systemic factors governing the healing response are pertinent. Significant avascular necrosis of juxta-articular bone seems to be a contraindication for this fixation system.

Second, the porous-surfaced material must not possess ingrowth inhibitory properties, that is, it must be biocompatible. Various materials fulfill this criterion: polymer,[31] ceramics,[32] ceramic-epoxy composites[33] and certain metals.[28-30] Suitability of these materials for clinical application is restricted by their strength, compliance, fatigue and corrosion and fabrication properties. Polymers are generally weak and lack durability, with low modulus; under dynamic loading, interfacial micromotion occurs, which is a deterrent to bone ingrowth. Fabrication characteristics of ceramic permit uniform porosity of desired size but it is brittle and fails by crack propagation.[34] Ceramic-epoxy composite (Cerosium) possesses improved deformation characteristics but degrades in vivo.[34] Of materials presently available, cobalt-chromium and titanium alloys show promise.

Alloys of Co-Cr in various forms have been used in humans for several years without discernible deleterious effects. A porous texture is achieved by sintering powder of Co-Cr beads onto the core implant. Histologic studies of bone-porous interface show minimal to no fibrous response.[35] Cobalt-chromium-molybdenum implants in soft tissue of rats did not show neoplastic induction at two years.[36] Wapner and associates[37] recently reported that chromium (VI) may suppress immune defenses in rats. Immunologic response and cross-reaction between cobalt and nickel have been seen in rabbits.[38] Increased local and systemic ion concentration has been noted but its significance is unknown. Although Co-Cr is strong and resistant to fatigue, the composite beaded layer is relatively brittle and may fail by crack propagation.[30]

Titanium, a relatively new metal in clinical use, seems to have certain advantages.[30,39] The configuration is a fibermesh of desired pore dimensions and density, achieved by sintering compacted titanium fibers to the implant. Its deformation property can be matched to trabecular bone and it does not fail by crack propagation. This theoretically results in more even stress distribution at bone-porous interface without associated pathologic bone remodeling. Titanium is well tolerated by host tissue and it appears to be accepted as part of the host tissue.[40] Increased local and systems ion concentration has been reported but its significance is unknown.[41] Surface area is increased 18-fold in this porous system.[39] At six weeks, titanium fibermesh-bone achieves the strength of cement-bone at operation.[39]

The third requirement for bone ingrowth is that the pore opening dimension be within a specific optimal range. Although data vary depending on material, laboratory animal model and static versus dynamic loading, this range seems to be 50 to 500 microns. Below 50 microns only fibrous ingrowth occurs[42]; above 500 microns (macropore size) fixation strength is achieved by contouring bone at irregular surface and not by bone ingrowth. The optimal range seems to be 50 to 250 microns, consistent with unit trabecular and osteonal dimension. In a ceramic-canine model, a pore size greater than 75 microns supported the haversian system.[43] If there is micromotion, the critical mean pore diameter for ingrowth is larger[44]; stability of the interface and the deformation property of porous material are variables.

The fourth requirement is that the bone-porous interface be intimate and stable (relatively free of motion). Motion results in fibrous ingrowth. If the interface is stable, small gaps (to 1.5 mm) may be bridged by bone.[35] The long-term stability of the interface is dependent on bone ingrowth but it takes three to six weeks to achieve substantial strength equal to immediate strength conferred by the cement system.[39] Immediate intraoperative stability is mandatory, achieved by a precision-interference fit of implant to bone.

An osteoconduction front progresses inward linearly with time. Given sufficient time, the thickness of the porous layer and provided osteoconductive conditions are met, ingrowth continues. This osteoconduction front undergoes maturation and remodeling, which are dependent on time, type of substrate bone (cortical or cancellous) and design (configurations of porous surface and core implant) and stress characteristics at the bone-pore interface. Mechanical properties of the porous-ingrowth composite parallel the extent and degree of maturation and remodeling.

That maturation and remodeling are time-dependent has been observed and is consistent with remodeling after bone injury. There are centripetal ingrowth and maturity gradient.[32] Cortical bone ingrowth, maturation and remodeling take longer than implant interfacing with cancellous bone, and are explained by the slower turnover of cortical bone.[45] Stress follows the paths of greatest stiffness. Inadequate implant material and design, which concentrate and shield stress, are expected to direct pathologic remodeling.[46,47]

The shear strength of bone-porous interface depends on the extent of bone-porous interface,[48] depth of ingrowth and maturation state of ingrown bone.[32] The weak link in this system is bone-porous interface. Shear tests regularly result in failure at this junction.[32] Shear strength of porous-trabecular bone composite is weaker than the porous-cortical system,[45] but trabecular bone strength can be increased with hypertrophy and cortical bone can be weakened with resorption. The ultimate interfacial shear strength does not exceed that of underlying bone.

Interface strength can be controlled by altering the material configuration. Shear strength is increased by increasing the number of porous layers.[49] This is attributed to three-dimensional bony interlock; it also confers increased strength in torsion[50] and tension.[49] A

porous system is distinctly superior to a cement system in these important modes of loading. In a pull-out test of porous-surfaced plates, there was little difference in shear strength for a pore size range of 50 to 400 microns.[49] Shear strength increases with time as a result of maturation of interlocking bone and increasing surface contact area and volume of ingrown bone.[32] Shear strength plateaus at six weeks[30,32] in dogs, which suggests a diminishing contribution of deeper ingrown bone to strength. Fibrous ingrowth yields significantly less strength than ingrowth bone. A porous implant in cortical bone possesses greater shear properties than the same implant in cancellous bone.[48]

The key consideration in the clinical application of porous systems is its durability under long-term dynamic loading. Titanium fibermesh on stemmed total hips implanted in dogs showed durable bony fixation (up to one year); ingrowth was regional around the stem,[39] probably reflecting regional variation in stress characteristics. Our understanding of the determinants of long-term dynamic stress-ingrowth is incomplete and is of critical importance in modeling optimal porous joints. Elucidation of the underlying biomechanical laws is under active investigation at UCLA Medical Center and other centers.

A previous study at UCLA Medical Center involved cemented-surface (stemless) total hip replacements in dogs. Delayed complications included loosening, neck fractures, pathologic bony remodeling and a variable fibrous membrane response at the bone-cement interface (Figure 16). Surface replacement arthroplasties in patients have been successful and are comparable with

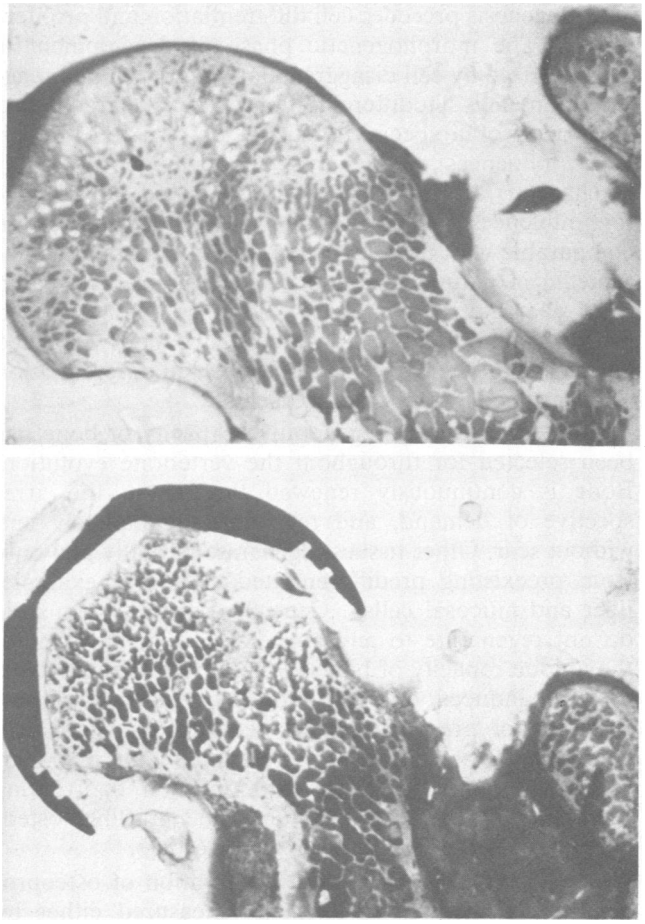

Figure 16.—Comparison of normal and cemented femoral surface replacement. **Top,** Ground section of normal canine femoral head. **Bottom,** Ground section of cemented surface replacement six months postoperatively. Note neck thinning and interposed fibrous membrane between cement and trabecular bone.

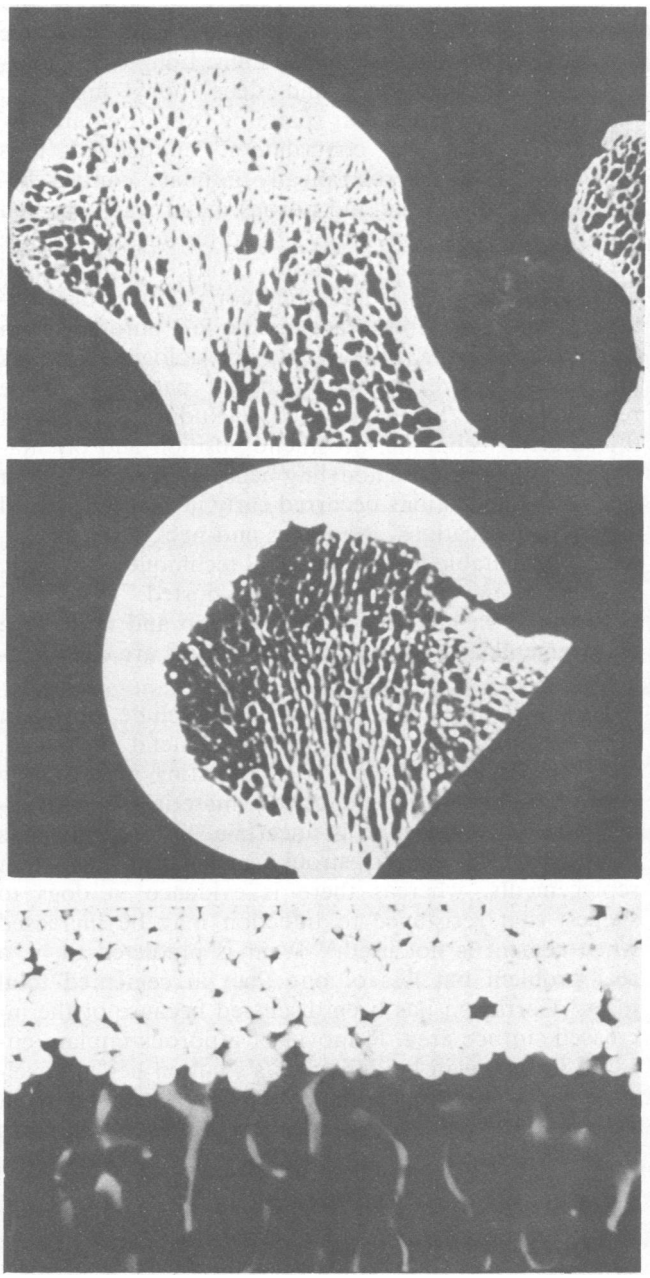

Figure 17.—Comparison of normal and porous femoral surface replacement. **Top,** A microradiograph of a normal canine femoral head. **Center,** A microradiograph of a porous femoral surface replacement two years postoperatively. Note the maintenance of normal trabecular density and pattern, indicating long-term biomechanical compatibility. **Bottom,** A magnified view of bony ingrowth into porous femoral cup. (Each pore diameter is approximately 200 microns.)

stemmed total hip replacements at UCLA. The complications have been similar to those in dogs, with an uneven stress transmission and membrane response.

A similar evaluation of long-term replacement in dogs has also been done.[47] The porous materials studied include sintered Co-Cr beads and titanium fibermesh. After implantation in hips, dogs were permitted free activity and were noted to be fully weight-bearing at the third week. Radiographs of hips were taken at regular intervals. The sacrifice schedule permitted time-dependent (up to two years) microradiographic and ground-section analyses of the bone-porous interface at the femoral head and acetabulum. Long-term specimens showed extensive and deep bony ingrowth; regional stress trabecular patterns were remarkably similar to those of contralateral unoperated hips (Figure 17). A microscopically intimate contact between trabecular bone and porous metal was observed (confirming a previous study)[30] and fibrous membranes were infrequent and minimal. Bony ingrowth and fibrous membrane may be a function of stress distribution. (In general, stress transmission in a porous system is presumed to be smooth and physiologic.) Factors influencing a stress pattern without pathologic bone remodeling are being analyzed, including the role of the surgical technique, prosthetic position and orientation and interfacial remodeling behavior to this implant design. Complications occurred early in the project and included dislocations, loosening and neck fractures directly attributable to poor surgical technique. The basic concept of porous ingrowth is supported. The short-term results in human porous total hip and total knee replacements at UCLA and other centers are encouraging.

Unknown areas of future concerns include long-term clinical durability, biocompatibility, metal corrosion, wear, infection and removal. Facilitating ingrowth by electrical stimulation and certain materials is interesting but the clinical role is uncertain.[51,52] Infection has been infrequent but disastrous in cemented total joint replacements, whereas there is evidence in dogs to suggest that resistance to infection may be increased when cement is not used.[53] Wear is predicted to be a real problem but less of one than in cemented total joints. Corrosion has been discussed because of the increased surface area. Removal of a porous implant encased in bone will be difficult; its solution lies in developing special instruments to minimize bone removal. Data now strongly support the soundness of a porous ingrowth concept and a hoped-for long-term durability.

Bone Morphogenetic Protein and Bone-Derived Growth Factors

MARSHALL R. URIST, MD:* In 1980 a UCLA Interdepartmental Conference on Growth Factors was organized by David W. Golde, MD.[44] Growth factors are growth-stimulating substances that are not nutrients. Metabolic substrates, cofactors, vitamins, amino acids and minerals are classified as nutrients rather than growth stimulants. Growth factors (also referred to as local hormones) are synthesized by a wide variety of tissues for stimulating DNA synthesis by the same or different cell type. At the 1980 conference, 12 different factors were known. More than ten additional growth factors have been reported since then, and the list is steadily growing. Included in this list are bone morphogenetic protein and bone-derived growth factor. Bone morphogenetic protein (BMP) is a component of bone tissue and its function is to induce differentiation of perivascular mesenchymal-type cells (pericytes) into osteoprogenitor cells, cartilage and bone.[55-60] Osteoprogenitor cells secrete bone-derived growth factor that stimulates DNA synthesis.[61-66] BMP and bone-derived growth factor are parts of the paracrine, a local-acting system as distinguished from the endocrine (long-distance-acting) system. The action of BMP and bone-derived growth factor is coefficient. BMP irreversibly induces a mesenchymal cell population to disaggregate, migrate, reaggregate and differentiate, whereas bone-derived growth factor reversibly stimulates osteoprogenitor cell proliferation and growth.

According to modern concepts of development, morphogenesis precedes cell differentiation and proliferation.[67] The morphogenetic phase of development is characterized by cell disaggregation, migration and reaggregation. The cytodifferentiation phase is characterized by growth of a specialized tissue or organ. Although BMP influences the genome, the detailed molecular mechanisms are not known. Bone-derived growth factor influences osteoprogenitor cells; the effects are comparable with those of other growth factors or somatomedin in nature. The aim of contemporary research is to characterize completely BMP and bone-derived growth factor and to make these two newly isolated agents available for research on bone cell differentiation and unsolved orthopedic problems.

The extraordinary regenerative capacity of bone has been selected for throughout the vertebrate evolution. Bone is continuously renewed throughout life, irrespective of demand, and regenerates completely and without scar. Other tissues regenerate partially and only from preexisting predifferentiated cells (for example, liver and mucosal cells). Central nervous system cells do not regenerate to any appreciable extent. Whether the unique capacity of bone to regenerate is attributable to BMP-induced differentiation of pericytes, to proliferation of preexisting bone cell precursors or to a combination of induced differentiation and precursor cell proliferation is the central question confronting researchers on fracture healing, bone grafting, osteoporosis and other skeletal system disorders.

The formation of bone by proliferation of osteoprogenitor cells is well known and measured either by reactions of endosteum and periosteum to bone injury or to alterations in dietary minerals and vitamins, or perturbations of the endocrine system, including parathyroid hormones and other hormones. The process of bone formation by BMP-induced cell differentiation is

*Professor of Orthopaedic Surgery, Bone Research Laboratory, UCLA School of Medicine.

less well known, and was not appreciated until bone matrix-induced bone formation was reported in 1965.[68]

Historically, four observations led to the present concept of bone morphogenetic protein. The first was the discovery that allogenic implants of demineralized bone matrix induced bone cell differentiation and formation of an ossicle filled with bone marrow.[69,70] The second was the finding that the BMP component of bone matrix was a chloroform-methanol, neutral salt-insoluble, 0.6N hydrochloride-insoluble, trypsin-labile protein.[55,71,72] The third step was the finding that BMP was a collagenase-resistant molecule, soluble and diffusible in body fluids at 37°C.[57] A fourth leap forward came with the discovery that BMP was soluble in 4 mol per liter of guanidine or 0.5 mol per liter of calcium chloride and 6 mol per liter of urea inorganic-organic solvent mixture, and had the essential properties of a hydrophobic molecule.[73-79]

Human BMP is a polypeptide with a molecular weight of 17,500, associated with two other low-molecular-weight (22,000 and 14,000) proteins, which are chemically extracted from the organic matrix including the cells of compact bone. The sources of bone morphogenetic protein are dentin matrix,[73] rat,[75] rabbit,[57] bovine[73] or human bone matrix[79] or mouse[61] and human[79] osteosarcoma tissues. How much of the BMP is derived from cells, cell membranes or extracellular matrix is not known. Prebone morphogenetic protein, probone morphogenetic protein and BMP may appear sequentially in the foregoing three loci. The BMP is assayed by implantation in a muscle pouch in the hindquarters of mice (Figure 18) or in skull trephine defects (Figure 19) in rats, dogs and monkeys. Implants of 5 mg of BMP induce formation of grossly visible bone deposits within two to three weeks. Qualitatively, human BMP and bovine BMP induce identical responses. Quantitatively, bovine BMP obtained from year-old steers is more active in lower doses than human BMP obtained from 20- to 60-year-old humans. In any case, the yield of new bone is directly proportional to the quantity of the implanted BMP. Bone morphogenetic protein is rapidly absorbed and sequentially replaced first by small round cells, macrophages, ameboid mesenchymal cells, spindle-shaped cells and then by hypertrophied connective tissue cells. By days 14 to 21, a fibrous envelope forms around the reactive connective tissue cells. Inside the envelope, differentiation of chondroid, cartilage and woven bone occurs. The chondroid and cartilage invariably grow in the avascular interior while the new bone develops on the vascularized exterior of the implant. During the interval from days 21 to 28, the woven bone is remodeled to produce a shell of lamellar bone filled with bone marrow.

The quantity of BMP relative to the total tissue weight is only 0.001% of cortical bone. The large bones of bovine and human species are almost unlimited in supply for the production of BMP by relatively inex-

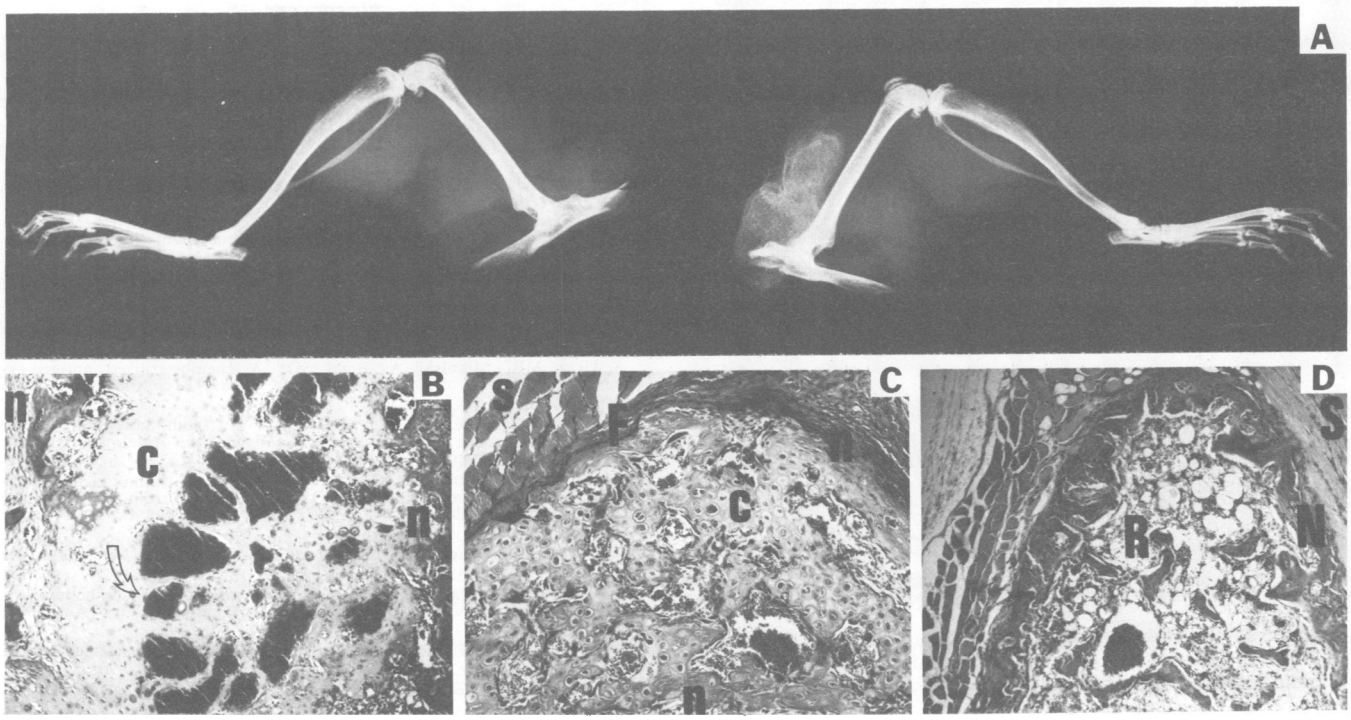

Figure 18.—A, Roentgenograms of the thighs of a mouse 21 days after implantation of 10 mg of human albumin **(left)** and 10 mg of human bone morphogenetic protein **(right).** Note the mass of new bone filling the anterior muscles of the right thigh. **B,** Photomicrograph of an implant of human bone morphogenetic protein in the mouse thigh 10 days after implantation of human bone morphogenetic protein **(arrow). C** = cartilage and chondro-osteoid, and **N** = new bone. **C,** Photomicrograph of an ossicle 15 days after implantation of bone morphogenetic protein showing replacement of bone morphogenetic protein with chondro-osteoid **(C)** and new bone **(N). F** = fibrous envelope and **S** = muscle. **D,** Photomicrograph of ossicle 21 days after implantation of bone morphogenetic protein. **R** = marrow cavity, **N** = cortex of new bone and **S** = muscle.

pensive conventional chemical methods.[79] BMP, derived from all presently known sources, is more completely extractable by guanidine hydrochloride (GuHCl) or calcium chloride ($CaCl_2$) urea inorganic-organic mixture than other solvents. The BMP is separated from high-molecular-weight proteins including gelatin peptides under dissociative conditions in 4 mol per liter of guanidine hydrochloride, and recovered with several other low-molecular-weight proteins by differential precipitation under associative conditions in 0.25 to 0.5 mol per liter of GuHCl. The proteins are then resolubilized, fractionated by gel filtration, preparative gel filtration or preparative gel electrophoresis and hydroxyapatite affinity chromatography, weighed and analyzed by SDS PAGE.

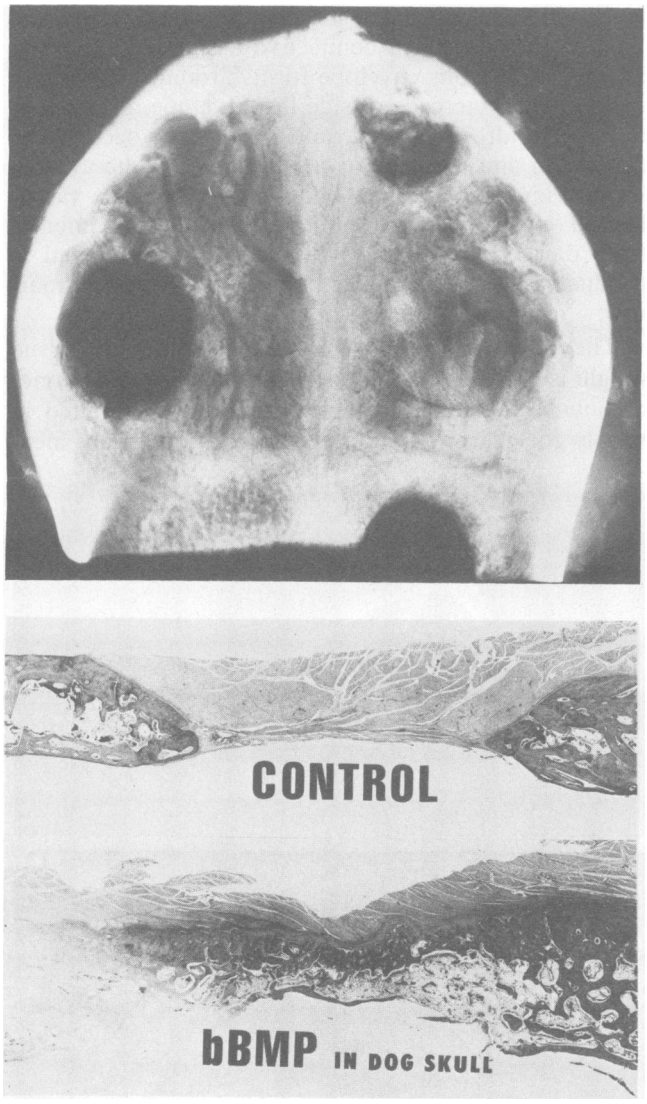

Figure 19.—A, Roentgenogram showing 2-cm skull trephine defects in an adult dog. The control defect on the left was implanted with 100 mg of albumin; the experimental defect on the right was implanted with 100 mg of bovine bone morphogenetic protein. Twelve weeks after the operation, the defect on the left is unhealed, while the one on the right is completely replaced with new bone. **B,** Photomicrograph of the trephine defects in the dog skull in Figure 19A, showing a membrane of fibrous tissue in the control and reconstitution of the skull with new bone and bone marrow in the bovine bone morphogenetic protein **(bBMP)**-treated defect.

Crude protein fractions with BMP activity include proteins with relative molecular masses of 14,000, 17,000, 22,000 and 34,000. All except the 17,500 protein can be removed without loss of BMP activity. The isolated 17,500 component is more rapidly absorbed and induces a lower yield of bone than the crude fractions. Differential analysis suggests that the 17,500 putative BMP, consisting of 20.8% acidic amino acids, is an acidic polypeptide. Monoclonal antibodies to this 17,500 protein have been produced in mice. A radioimmunoassay of BMP is being developed. The *N*-terminus amino acid sequence of each of the low-molecular-weight proteins associated with BMP is under investigation. The possibilities for BMP production by DNA recombinant technology are considerable.

Interesting prospects for the future are for bone morphogenetic protein as a tool for fundamental research on cell differentiation and for investigation of more than 100 bone diseases of unknown causes. That BMP could be the probe for an area as significant as cell differentiation is not unexpected when it is recognized that bone is the hallmark of vertebrate species, developing from mesoectoderm early in embryonic life and regenerating completely and flawlessly throughout all of postfetal life.

REFERENCES

1. McCewen W: Observations concerning transplantation of bone. Proc R Soc Lond 1881; 32:232

2. Lexor E: Die Verwendung der Freien Knochemplastic Nebst Versechen Über Gelenkversteifung und Gelenktransplantatum. Arch Klin Chir 1908; 86:939

3. Inclan A: Use of preserved bone graft in orthopaedic surgery. J Bone Joint Surg [Am] 1942; 24:81-96

4. Parrish FF: Allograft replacement of all or part of the end of a long bone following excision of a tumor: Report of 21 cases. J Bone Joint Surg [Am] 1973; 55:1-22

5. Mankin HJ, Fogelson FS, Trasher AZ, et al: Massive resection and allograft transplantation in the treatment of malignant bone tumors. N Engl J Med 1976; 294:1247-1255

6. Mankin HJ, Doppleit SH, Sullivan TR, et al: Osteoarticular and intercalary allograft transplantation in the management of malignant tumors of bone. Cancer 1982; 50:613-630

7. Burchardt H, Enneking WF: Transplantation of bone. Surg Clin North Am 1978; 58:403-427

8. Urist MR, Mikulski A, Boyd SD: A chemosterilized antigen-extracted autodigested alloimplant for bone banks. Arch Surg 1975 Apr; 110:416-428

9. Grant TT, Eilber FE, Johnson EE, et al: Limb Salvage in Osteosarcoma. Read before the 48th Annual Meeting of the American Academy of Orthopaedic Surgeons, Las Vegas, March 2, 1981

10. Brighton CT, Black J, Friedenberg ZB, et al: A multicenter study of the treatment of non-union with constant direct current. J Bone Joint Surg [Am] 1981; 63:2-13

11. Bassett CAL, Mitchell SN, Gaston SR: Treatment of ununited tibial diaphyseal fractures with pulsing electromagnetic fields. J Bone Joint Surg [Am] 1981 Apr; 63:511-523

12. Weiland AJ, Daniel RK: Microvascular anastomoses for bone grafts in the treatment of massive defects in bone. J Bone Joint Surg [Am] 1979; 61:98-104

13. Pho RW: Free vascularized fibular transplant for replacement of the lower radius. J Bone Joint Surg [Br] 1979; 61:362-365

14. Charnley J: Low friction arthroplasty. Clin Orthop 1970; 72:7-21

15. Charnley J: Low Friction Arthroplasty of the Hip: Theory and Practice. Berlin, Springer Verlag, 1979

16. Cupic Z: Long-term follow-up of Charnley arthroplasty of the hip. Clin Orthop 1979; 141:28-43

17. Beckenbaugh RD, Ilstrup DM: Total hip arthroplasty—A review of 333 cases with long follow-up. J Bone Joint Surg [Am] 1978 Apr; 60: 306-313

18. Salvati EA, Wilson PD Jr, Jolley MN, et al: A ten-year follow-up study of our first 100 consecutive Charnley total hip replacements. J Bone Joint Surg [Am] 1981; 63:753-767

19. Moreland JR, Gruen TA, Mai L, et al: Aseptic loosening of total hip replacement: Incidence and significance, chap 13, *In* Riley LH Jr (Ed): The Hip—Proceedings of the 8th Open Scientific Meeting of The Hip Society, 1980. St Louis, CV Mosby, 1980, pp 281-291

20. Ling RSM: Prevention of loosening of total hip components, *In* Riley LH Jr (Ed): The Hip: Proceedings of the 8th Open Scientific Meeting of The Hip Society, 1980. St. Louis, CV Mosby, 1980, pp 292-307

21. Amstutz HC, Graff-Radford A: THARIES approach to surface replacement of hip, *In* Murray DG (Ed): Instructional Course Lectures, Vol 30. The American Academy of Orthopaedic Surgeons. St Louis, CV Mosby, 1981, pp 422-443

22. Cracchiolo A III, Benson M, Finerman GA, et al: A prospective comparative clinical analysis of the first-generation knee replacements: Polycentric vs geometric knee arthroplasty. Clin Orthop 1979 Nov-Dec; 145:37-46

23. Insall J, Scott WN, Ranawat CS: The total condylar knee prosthesis —A report of 220 cases. J Bone Joint Surg [Am] 1979; 61:173-180

24. Amstutz HC, Sew Hoy AL, Clarke IC: UCLA anatomic shoulder arthroplasty. Clin Orthop 1981; 155:7-20

25. Wolff J: Über die innere Architektur der Knochen und ihre Bedeutung für die Frage von Knochenwachstum. Virchows Arch [Klin Med] 1870; 50:389-453

26. Hedley AK, Clarke IC, Bloebaum RD, et al: Viability and cement fixation of the femoral head in canine hip surface replacement (Otto Aufranc Award paper), *In* The Hip—Proceedings of the 7th Open Scientific Meeting of The Hip Society, 1979. St Louis, CV Mosby, 1979, pp 160-187

27. Chandler HP, Reineck FT, Wixson RL, et al: Total hip replacement in patients younger than thirty years old--A five-year follow-up study. J Bone Joint Surg [Am] 1981 Dec; 63:1426-1434

28. Hirschhorn JS, Reynolds JT: Powder metallurgy fabrication of cobalt alloy surgical implants, *In* Korostoff E (Ed): Research in Dental and Medical Materials. New York, Plenum Press, 1969, pp 137-150

29. Pilliar RM, Cameron HU, Macnab I: Porous surface layered prosthetic devices. J Biomed Eng 1975; 10:126-131

30. Galante J, Rostoker W, Lueck R, et al: Sintered fiber metal composites as a basis for attachment of implants to bone. J Bone Joint Surg [Am] 1971; 53:101-114

31. Struthers AM: An experimental study of polyvinyl sponge as a substitute for bone. Plast Reconstr Surg 1955; 15:274-289

32. Nilles JL, Coletti JM, Wilson C: Biomechanical evaluation of bone —Porous material interface. J Biomed Mater Res 1973; 7:231-251

33. Peterson CD, Miles JS, Solomons C, et al: Union between bones and implants of open pore ceramic and stainless steel: A histologic study. J Bone Joint Surg [Am] 1969; 51:805

34. Welsh RP, Pilliar RM, Macnab I: Surgical implants—The role of surface porosity in fixation to bone and acrylic. J Bone Joint Surg [Am] 1971 Jul; 53:963-977

35. Cameron HU, Pilliar RM, Macnab I: The effect of movement on the bonding of porous metal to bone. J Biomed Mater Res 1973; 7:301-311

36. Cameron HU, Pilliar RM, Macnab I: Porous vitallium in implant surgery. J Biomed Mater Res 1974; 8:283-289

37. Wapner KL, Black J, Morris D: Chromium release by cast Co-Cr alloy in vivo: Ionic valence and its implications for morbidity (Abstract). Trans Ortho Res Soc 1983; 8:240

38. Merritt K, Brown SA: Metal sensitivity reactions to bone screws in rabbits, *In* Lee AJC, Albrektsson T, Branemark P-I (Eds): Clinical Applications of Biomaterials—Advances in Biomaterials, Vol 4. New York, John Wiley & Sons, 1982, pp 85-91

39. Lembert E, Galante J, Rostoker W: Fixation of skeletal replacement by fiber metal. Clin Orthop 1972; 87:303-310

40. Albrektsson T, Branemark P-I, Hansson H-A, et al: Ultrastructural analysis of the interface zone of titanium and gold implants, *In* Lee AJC, Albrektsson T, Branemark P-I (Eds): Clinical Applications of Biomaterials—Advances in Biomaterials, Vol 4. New York, John Wiley & Sons, 1982, pp 167-177

41. Woodman JL, Jacobs JJ, Galante JD, et al: Titanium release from fiber metal composites in baboons—A long-term study (Abstract). Trans Ortho Res Soc 1982; 7:166

42. Spector M, Harmon SL, Kreutner A: Characteristics of tissue growth into proplast and porous polyethylene implants in bone. J Biomed Mater Res 1979; 13:677-692

43. Hulbert SF, Klawitter JJ, Talbert CD, et al: Materials of construction for artificial bone segments, *In* Korostoff E (Ed): Research in Dental and Medical Materials. New York, Plenum Press, 1969, pp 19-67

44. Ducheyne P, de Meester P, Aernoudt E: Influence of a functional dynamic loading on bone ingrowth into surface pores of orthopedic implants. J Biomed Mater Res 1977 Nov; 11:811-838

45. Klawitter JJ, Weinstein AM: The status of porous materials to obtain direct skeletal attachment by tissue ingrowth. Acta Orthop Belg 1974; 40:755-765

46. Pilliar RM, Cameron HU, Binnington AG, et al: Bone ingrowth and stress shielding with a porous surface coated fracture fixation plate. J Biomed Mater Res 1979; 13:799-810

47. Hedley AK, Clarke IC, Kozin SC, et al: Porous ingrowth fixation of the femoral component in a canine surface replacement of the hip. Clin Orthop 1982; 163:300-311

48. Clemons AJT, Weinstein AM, Klawitter JJ, et al: Interface mechanics of porous titanium implants. J Biomed Mater Res 1981; 15:73-82

49. Bobyn JD, Pilliar RM, Cameron HU, et al: The effect of porous surface configuration on the tensile strength of fixation of implants by bone ingrowth. Clin Orthop 1980; 149:291-298

50. Hahn M, Palich W: Preliminary evaluation of porous metal surface titanium for orthopedic implants. J Biomed Mater Res 1970; 4:571-577

51. Ducheyne P, Hench LL, Kagan A, et al: Effect of hydroxyapatite impregnation on skeletal bonding of porous coated implants. J Biomed Mater Res 1980; 14:225-237

52. Collela SM, Miller AG, Stang RG, et al: Fixation of porous titanium implants in cortical bone enhanced by electrical stimulation. J Biomed Mater Res 1981; 15:37-46

53. Samuelson KM, Daniels AU, Rasmussen GL, et al: Evaluation of cemented versus cementless fixation and infection in canine total joint arthroplasties (Abstract). Trans Ortho Res Soc 1983; 8:230

54. Golde DW, Herschman HR, Aldons JL, et al: Growth factors. Ann Intern Med 1980; 92:650-662

55. Urist MR, Strates BS: Bone morphogenetic protein. J Dent Res 1971; 50(Suppl 6):1392-1406

56. Urist MR, Iwata H, Ceccotti PWL, et al: Bone morphogenesis in implants of insoluble bone gelatin. Proc Natl Acad Sci USA 1973; 70: 3511-3515

57. Urist MR, Mikulski A, Lietze A: Solubilized and insolubilized bone morphogenetic protein. Proc Natl Acad Sci USA 1979; 76:1828-1832

58. Urist MR, Mikulski AJ: A soluble bone morphogenetic protein extracted from bone matrix with a mixed aqueous and nonaqueous solvent. Proc Soc Exp Biol Med 1979; 162:48-53

59. Urist MR: New bone formation induced in postfetal life by bone morphogenetic protein, *In* Becker RO (Ed): Mechanisms of Growth Control. Springfield, Ill, CC Thomas, 1981, pp 406-434

60. Urist MR, Conover MA, Lietze A, et al: Partial purification and characterization of bone morphogenetic protein, *In* Cohn D, Talmage R, Matthews JL (Eds): Hormonal Control of Calcium Metabolism—Proceedings of the 7th International Conference on Calcium Regulating Hormones. The Netherlands, Excerpta Medica 1981, pp 307-314

61. Urist MR, Lietze A, Mizutani H, et al: A bovine low molecular weight bone morphogenetic protein (BMP) fraction. Clin Orthop 1982 Jan-Feb; 162:219-232

62. Canalis E, Peck WA, Raisz LG: Stimulation of DNA and collagen synthesis by autologous growth factor in cultured fetal rat calvaria. Science 1980; 210:1921-1923

63. Howard GA, Bottemiller BL, Baylink DJ: Evidence for the coupling of bone formation to bone resorption in vitro. Metab Bone Dis Res 1980; 2:131-135

64. Kato Y, Watanabe R, Hiraki Y, et al: Selective stimulation of sulfated glycosaminoglycan synthesis by multiplication-stimulating activity, cartilage-derived factor and bone-derived growth factor: Comparison of their actions on cultured chondrocytes with those of fibroblast growth factor and rhodomine fibrosarcoma-derived growth factor. Biochim Biophys Acta 1982; 716:232-239

65. Drivdahl RH, Puzas JE, Howard GA, et al: Regulation of DNA synthesis in chick calvaria cells by factors from bone organ culture (41249). Proc Soc Exp Biol Med 1981; 168:143-150

66. Farley JR, Masuda T, Wergedal JE, et al: Characterization of the mitogenic effect on bone cells in vitro. Biochemistry 1982; 21:3508-3513

67. Zwilling E: Morphogenetic phases in development. Dev Biol 1968; 2(Suppl):184-207

68. Urist MR: Bone: Formation by autoinduction. Science 1965; 150: 893-899

69. Urist MR: The substratum for bone morphogenesis. Dev Biol 1970; 4(Suppl):125-163

70. Urist MR, Silverman BF, Buring K, et al: The bone induction principle. Clin Orthop 1967; 53:243-283

71. Urist MR, Dowell TA, Hay PH, et al: Inductive substrates for bone formation. Clin Orthop 1968 Jul-Aug; 59:59-96

72. Urist MR, Earnest F, Kimball KM, et al: Bone morphogenesis in implants of residues of radioisotope labelled bone matrix. Calcif Tissue Res 1974; 15:269-286

73. Urist MR, Iwata H: Preservation and biodegradation of the morphogenetic property of bone matrix. J Theor Biol 1973 Jan; 38:155-168

74. Urist MR, Iwata H, Boyd SD, et al: Observations implicating an extracellular enzymic mechanism of control of bone morphogenesis. J Histochem Cytochem 1974; 22:88-103

75. Conover MA, Urist MR: Dentin matrix bone morphogenetic protein, *In* Veis A (Ed): The Chemistry and Biology of Mineralized Connective Tissues, Proceedings of the 1st International Conference on the Chemistry and Biology of Mineralized Connective Tissues, Northwestern University Dental School, Chicago, May 3-7, 1981. New York, Elsevier/ North-Holland, 1982, pp 597-606

76. Hanamura H, Higuchi Y, Nakagawa M, et al: Solubilized bone morphogenetic protein (BMP) from mouse osteosarcoma and rat demineralized bone matrix. Clin Orthop 1980; 148:281-290

77. Bauer FCH, Urist MR: Human osteosarcoma-derived soluble bone morphogenetic protein. Clin Orthop 1981; 154:291-295

78. Urist MR, DeLange R, Finerman GAM: Bone cell differentiation and growth factors: Induced activity of chrondroosteogenetic DNA. Science 1983 May 13; 220:680-686

79. Urist MR, Sato K, Brownell AG, et al: Human bone morphogenetic protein (hBMP). Proc Soc Exp Biol Med 1983 Jun; 173:194-199